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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,907	02/25/2004	Bjarne Bogen	36731S-000001/US	6743

27572 7590 11/18/2008

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008 and 13 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77,83-95,97-108 and 118-123* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,97 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83, 88-92, 95, 98-100 and 118-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-37, 77, 83-95, 97-108, and 118-123 are all the pending claims for this application.

2. Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

3. Claim 83 was amended in the Response of 7/10/08 and 8/13/08, Claims 88-92, 95, 98-100, 118, 121 and 122 were amended in the Response of 7/10/08 and Claims 96 and 124-126 are cancelled in the Response of 7/10/08.

4. Claims 83, 88-92, 95, 98-100 and 118-123 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection.

Withdrawal of Objections

Claim Objections

6. The objection to Claim 83 for reciting in the second "wherein" clause "said monomer unit each" is withdrawn in view of the amendment to recite "each of said monomer unit".

7. The objection to Claims 96 and 98 as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of cancelled Claim 96.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

8. The rejection of Claims 83, 88-92, 95, 96, 98-100 and 118-126 under 35 U.S.C. 101 because the claims read on a nucleic acid that is found in nature is withdrawn in view of the amendment of the claims to recite an isolated nucleic acid.

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 83, 88-92, 95, 96, 98-100 and 118-126 for the recitation "said monomer unit each comprises an antigenic unit and a targeting unit for an antigen presenting cell" in Claim 83 is withdrawn in view of the amendment of Claim 83 to recite that the monomer unit comprises a targeting unit for an APC and an antigenic unit.

10. The rejection of Claim 100 for the recitation "wherein said antigenic scFv is identical to a monoclonal Ig produced by myeloma or lymphoma" is withdrawn in view of the amendment of the claims to indicate that the VH and VL domains for the scFv are from a monoclonal Ig.

11. The rejection of Claim 118 in lacking antecedent basis for the limitation "said recombinant antibody-based molecule" is withdrawn in view of the amendment to recite the recombinant antibody-based dimeric molecule.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

12. The rejection of Claims 118 (and 120) under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record as set forth in the Office Actions of 11/7/06, 7/19/07 and 4/10/08.

Upon further consideration, claim 120 has been joined under this rejection because in being drawn to any vector, the vector is not distinguishable from an enabled vector in the specification or one being isolated in vitro from one found in vivo.

In the Office Action of 7/19/07, the Examiner stated that the specification is not enabling for the full scope of the claims because:

"The specification does not teach gene immunization (or gene therapy) methods for treating or *preventing* a cancer much less a myeloma or lymphoma or inducing a *prophylactic* T- or B-cell immune response in a *human patient* with a *nucleic acid* of the claims examined in the Office Action of 11/7/06, the vector comprising the nucleic acid or a vector-transfected cell or cell line encoding the recombinant antibody-based molecule. There are no working examples in Applicant's specification to guide the skilled artisan in practicing the administration of the nucleic acid, vector or transfected host cell, more especially by injection and electroporation, which results in *a) induction of an immune B- and T cell response* or *b) a reduction in a cancer such as myeloma or lymphoma*. The goal of tumor vaccination is the induction of tumor immunity to *prevent* tumor occurrence or recurrence and Applicants have not demonstrated any such effect(s) with the nucleic acid as originally examined."

In the Office Action of 4/10/08, the Examiner maintained the rejection as follows:

"a) Applicants' allegations on pp. 18-24 of the Response of 1/22/08 and copies of the cited references (Stevenson (2004); Eisen (1968); Schulenburg (1971); Eisen (1985); Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); and Fredriksen (2006)) have been considered and are not found persuasive.

Applicants allege the claims are fully enabled for the scope of Vaccibody embodiments because: expression product for specific Vaccibody protein to idiotypic Fv from the murine MOPC315.4 tumor (i.e., the antigenic unit is an idiotype derived from the murine multiple myeloma MOPC315.4 cell line) was detected in sera of mice (Example 5 on pp. 34-35 of the specification); methods for using the pharmaceutical compositions to treat and prevent myeloma showing intra-muscular injection and electroporation for expression in vivo (p. 28 of the specification and Examples 5 and 6; citing Stevenson (2004) as support for established route of injection); the murine MOPC315.4 multiple myeloma animal model is correlative and predictive for treatment and prevention of multiple myeloma in other animals (citing Eisen (1968), Schulenburg (1971) and Eisen (1985)); the term "vaccine connotes prevention and/or diminishment of a disease in comparison to no vaccine at all"; the specification describes procedures for administering Vaccibody to produce a protective effect and the generation of a protective effect against development of tumors (Figures 21a and 21b; 22 and 23); and further evidence of prophylactic and preventative effects of the pharmaceutical and vaccine compositions (Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); Fredriksen (2006)).

Examiner's Reply

The Examiner appreciates the detailed explanation, the copies of the reference articles, and the technical effort into characterizing a single vaccibody embodiment, namely, that for generating an anti-idiotypic response against the monoclonal antibody-producing murine MOPC315.4 multiple myeloma in the mouse model in vivo in the specification, and the addition studies for Id vaccines described in the references.

Applicants have established the credibility of the murine MOPC315.4 multiple myeloma mouse model;

Applicants have established with the Id Vaccibody, that a prophylatic and therapeutic effect could be generated against the mouse MOPC315.4 tumor in vivo to block tumor progression by generating an anti-idiotypic response with the VH/VL idiotype of the Vaccibody.

Schjetne (2007) establishes that a clonotypic CD40-expressing tumor in mice could be targeted with Ig-like vaccine construct directed against CD40;

Fredriksen (2006) appears to be the publication of the data presented in the instant specification; and

Fredriksen (2007) establishes that a clonotypic tumor in mice (B lymphoma (A20)) or MOPC315) could be targeted with an Ig-like vaccine construct targeting MIP-1alpha and RANTES.

Notably and significantly, Applicants have not shown that the similar results for generating an anti-idiotype response that was both therapeutic and prophylactic could be generated against for example a human xenograft of multiple myeloma or lymphoma cells in an animal model. Further, Applicants have not shown that the myriad combinations of antigenic units and targeting units for a single monomeric unit encompassed by the claims have actually been used in a construct, administered to an animal model bearing any relevant disease much less multiple myeloma or lymphoma in order to generate a) both a T-cell and B-cell immune response, b) an immunologically effective response against MM or lymphoma, where the response was therapeutic and/or preventative.

The examiner submits that one of ordinary skill in the art could not reasonably make the correlation or prediction that from a single animal model using a single clonotypic tumor with a single Vaccibody, that any Vaccibody embodiment could be used in vivo to treat or prevent any disease much less multiple myeloma in any animal including a human. Applicants' entire presentation does not provide sufficient enablement to practice the scope of the inventive claims.

Examiner draws Applicants attention to the critically important work of Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7)

metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not even necessarily correlate with results expected in human multiple myeloma or lymphoma.

For all of the foregoing reasons, this aspect of the rejection is maintained.

b) Applicants' allegations on pp. 24-25 of the Response of 1/22/08 have been considered and are found persuasive.

Applicants' admission on the record is that the "dimmers" ["dimers"] in the present application are formed from homodimers, which assemble spontaneously from the expression products of one single vector (due to the presence of the dimerization unit in the monomers). It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work."

Applicants' allegations on pp. 13-16 of the Response of 7/10/08 have been considered and are not found persuasive. Applicants allege "With respect to Claim 118, the claim language merely requires that the isolated nucleic acid fragment of Claim 83 be formulated "to be administered to a patient to induce production of said antibody based dimeric molecule" and that the injection of the isolated nucleic acid molecule in a "patient" leads to production in the patient of the expression product of the isolated nucleic acid molecule. Hence, Claim 83 does not require that the patient raise an immune response against the expression product. Finally Applicants allege the art pertaining to nucleic acid vaccination, has amply demonstrated that expression of an injected nucleic acid molecule can be easily accomplished.

Response to Arguments

In the interest of expediting prosecution, all of the examiner's foregoing comments are re-iterated and incorporated in full. Arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03). Further, Applicants assertion that the general state of the art for nucleic acid vaccination is enabled is not supported by extrinsic evidence. Pursuant to MPEP 2144.03, "ordinarily

there must be some form of evidence in the record to support an assertion of common knowledge."

Applicants are invited to supplement the record with extrinsic evidence to support the argument that any nucleic acid vaccination much less the full scope of the claims is enabled. Alternatively, Applicants are invited to amend the claims to read on what is reasonably enabled by the specification in using the nucleic acid to generate expression of the dimeric antibody molecule in vivo. The examiner submits that one of ordinary skill in the art could not reasonably make the correlation or prediction that from a single working animal model using a single example of a nucleic acid encoding a single Vaccibody embodiment in the specification, that any nucleic acid encoding any Vaccibody meeting all of the instant claim limitations (i.e., to the extent they are encompassed in Claim 83) could even be expressed or to what measurable extent the Vaccibody could be expressed in vivo. Applicants' entire presentation thus far does not provide sufficient enablement to practice the full scope of the inventive claims.

New Grounds for Objection

Claim Objections

13. Claims 83 and 95 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 83 is drawn to "a targeting unit for an antigen presenting cell" and Claim 95 is drawn to "said

targeting unit have the ability to target antigen presenting cells (APC)." The claims are interpreted as being reasonably similar enough to be duplicative.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 88-92 and 98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 88-92 and 98 are indefinite because they are drawn to a targeting unit that can recognize a corresponding binding partner on a broader genus of cells than an APC. Thus, the claims are considered as broadening limitations from Claim 83 which requires that the targeting unit is for an APC only. For example, Claim 88 is drawn to the targeting unit itself being any ligand without identifying which APC-specific ligand is intended. Further, Claim 89 is drawn to the targeting unit being for soluble CD40 ligand or a chemokine. It is not clear how the targeting unit is specific to APCs when, for example, chemokine receptors may be expressed on APCs and non-APCs alike. How can the targeting unit be specific for only APCs when the targeting unit itself could potentially recognize other cells than APCs?

Reinstatement of the 102(e) Rejection from the Office Action of 11/7/06

15. The Examiner has reconsidered the scope of the newly amended claims. Upon further reconsideration, it is now the Examiner's position that certain disclosures in Herman were overlooked during the prosecution proceeding, and the rejection is hereby re-instated as discussed below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 83, 88-92, 95, 98-100, and 118-123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003; cited in the PTO 892 form of 11/7/06).

Claims 83, 88-92, 95, 98-100, and 118-123 are *interpreted* as being drawn to a nucleic acid encoding a monomeric unit for recombinant antibody-based dimeric molecule, wherein each monomeric unit comprises a targeting unit for binding an APC, a dimerization motif and an antigenic unit all being operably linked, where the dimerization motif comprises an Ig hinge and a Cgamma3 domain (and no CH2 domain) and the dimerization motif of each monomer contributes to the dimerization by disulfide

bonding between the Ig hinge and hydrophobic interactions between the Cgamma3 domains (Claims 83 and 95), where the targeting unit is a ligand (Claim 88) comprising soluble CD40 ligand (Claims 89) or a chemokine (Claims 89) such as RANTES or MIP-1α (Claims 90-92), where the targeting unit can target a chemokine receptor (Claim 98) and the antigenic units is an antigenic scFv with the VH and VL from a monoclonal Ig produced by a myeloma or lymphoma (Claims 99 and 100), and the nucleic acid is formulated for administering to a subject (Claim 118), and vectors comprising the nucleic acid (Claim 119), and a cell line transfected with the vectors (Claim 120), and compositions comprising the nucleic acid, the vector or the cell (Claims 121 and 122) and a kit comprising the nucleic acid to produce the antibody-based molecule (Claim 123).

Herman discloses nucleic acids, vectors comprising nucleic acids and vector transfected cell lines encoding a multispecific ligand comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusions of the antibody to other functional moieties (eg. toxins, cytokines, chemokines, streptavidin, adhesion molecules) [0107-0108], where the multispecific ligand comprises an Fc portion and an Ig hinge portion. An Fc portion may be a partial Fc portion (eg. minibody-CH3) [0069]. The amino acid composition (including length) of the hinge portion should provide means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper, fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide

bonds eg. IgG3) [0116]. The binding characteristics of the multispecific ligand e.g., scfv, is that the target ligand is of sufficient affinity to effectively bind or remain bound without the other unit being available for simultaneous binding [0119]. An example of one monomer comprises a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity (for example a diseased or disease-causing or mediating cell or infectious agent) and a second ligand binding moiety that recognizes a target ligand and wherein the first target ligand is characterized in that it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety [0122].

Herman discloses the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a ligand which effects binding to another immune cell, for example a T cell or APC. The multispecific ligand is a tetraspecific antibody or the first moiety binds to but is incapable of modulating the activity of an immune cell and the second moiety modulates the activity of the immune cell independently of the first moiety [0137].

Herman discloses a multispecific ligand which comprises a first ligand binding moiety which neutralizes a ligand eg. a natural ligand such as a chemokine and a second ligand binding moiety which binds to a cell marker associated with a cell [0138]. Examples of proteins which are targeted by multispecific ligand (targeting unit) include CD40 [0164], MIP-1 alpha and RANTES [0428]. Herman discloses a multispecific ligand comprising an anti-idiotype antibody (antigenic unit) so as to facilitate a desired immune response eg. vaccination type responses [0172, 0252]. For one embodiment, Herman

discloses a multispecific ligand containing an immunocytokine containing an anti-idiotypic antibody component and a cytokine component [0018]. Herman discloses nucleic acids, expression vectors and host cells expressing the vectors to produce a multispecific ligand [0241- 0298; 0314-0319]. Herman discloses a kit comprising one or more polynucleotides comprising one or more DNA sequences, where the DNA sequences encode one or more polypeptides which are sufficient to constitute a multispecific ligand as defined in any of the preceding paragraphs [0424].

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Partial Signatory Authority